Chapter

The Role of Functional Electrical Stimulation in Brachial Plexus Injury Repair

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Abstract

Brachial plexus injury (BPI) is a type of peripheral nerve injury, which is mainly manifested as upper limb sensory and motor dysfunction. Although the injury will not endanger life, it can cause serious functional loss and high disability rate, and eventually lead to patients unable to live normally. At present, the treatment methods for BPI mainly include conservative treatment, such as limb massage, exercise, drug therapy, autonomous movement and strength training; In clinic, nerve repair, nerve transplantation and muscle transfer can also be used. Although surgical treatment can better restore the function of injured brachial plexus, there is a certain risk, so it is not the first choice of treatment. As a mature electrical stimulation method, functional electrical stimulation (FES) can play a good role in promoting injured nerve regeneration and preventing skeletal muscle denervation atrophy, so it can be widely used in the treatment and functional recovery of BPI. This article will review the research progress of FES in the treatment of BPI.

Keywords: brachial plexus injury, functional electrical stimulation, research progress, clinical application, mechanism of action

1. Introduction

Brachial plexus injury (BPI) is a common type of peripheral nerve injury. In addition to muscle paralysis, motor and skin sensory functions will decrease or disappear in its innervated area, which has a high disability rate. In recent years, with the continuous occurrence of excessive stretching and traffic accidents, the incidence of BPI has also become higher and higher. Although the progress of peripheral nerve surgery has significantly improved the treatment effect of BPI, scar will be produced at the nerve repair site, which will inevitably distort the contour of nerve pulse reaching the sensory and motor cortex, and eventually make the injured peripheral nerve unable to regenerate effectively. Some regenerated axons will not be able to reach the receptors affected by the scar interface, and other relatively normal axons will also be misled, so that they can only re-dominate the wrong scar sensory receptors or irreversibly degenerate receptors, which will lead to impaired sensory function of shoulder joint and upper limb with loss of muscle strength [1]. Therefore, it is particularly important to find an effective method to improve the dysfunction after BPI.

In 1961, American expert liberson [2] first proposed functional electrical stimulation (FES) therapy, which belongs to the category of neuromuscular electrical stimulation (NMES). FES is mainly based on the patient's condition to set up the program in advance, and place the electrode on one or more groups of muscles of the patient's affected limb, and then the paralyzed muscles will contract under the stimulation of a certain intensity of low-frequency pulse current, so as to induce muscle movement or simulate normal autonomous movement (such as upper limb grasping, lower limb walking and other functional activities) At the same time, the repeated movement pattern information can be transmitted to the central nervous system, forming excitement marks on the cortex, and ultimately can achieve the purpose of restoring muscle movement and enhancing balance ability [3]. In 2015, Elzinga et al. [4] found that nerve repair is needed after nerve injury. If the time of nerve repair is appropriately prolonged and FES is used to stimulate motor and sensory neurons for a long time, the speed of nerve growth can be improved, and nerve fibers can grow into the innervated skeletal muscle accurately along the direction of electric field. As one of the promising therapeutic technologies in the field of modern clinical rehabilitation, FES can be used to treat BPI, play the role of promoting regeneration of injured brachial plexus and preventing denervated atrophy of skeletal muscle.

2. Clinical anatomy of the brachial plexus

2.1 Composition of brachial plexus

The brachial plexus is a collection of most of the nerve fibers of the 5th-8th cervical nerve anterior branch and the 1st thoracic nerve anterior branch, usually composed of five roots, three stems, six strands and three bundles. The 5 nerve roots from the spinal cord exit the intervertebral foramen at the same time as they branch out the dorsal scapular nerve (C_{4-5}), the long thoracic nerve (C_{5-7}), and the phrenic nerve (C_{3-5}). The five nerve roots form the superior, middle and inferior trunks on the lateral edge of the anterior scalene muscle, among them, C_{5-6} constitutes the superior trunk, C_7 independently constitutes the middle trunk, and C_8-T_1 constitutes the inferior trunk. Each trunk is divided into anterior and posterior divisions above or behind the clavicle. The anterior division of the upper and middle trunks synthesize the lateral cord, and the main branches are the lateral root of median nerve, musculocutaneous nerve and lateral pectoral nerve; the anterior division of the lower trunk synthesize the medial cord, and the main branches are the medial antebrachial cutaneous nerve, ulnar nerve and medial root of median nerve; the posterior division of the three trunks converges into the posterior cord, the main branches are the subscapular nerve, thoracodorsal nerve, axillary nerve and radial nerve. The three bundles enter the axillary and send out nerve branches, which mainly control the sensory and motor functions of the upper limbs, shoulder back and chest (**Figure 1**) [5].

2.2 Major neural injury and its clinical expressions

BPI can generally be divided into upper brachial plexus injury, lower brachial plexus injury and complete brachial plexus injury [6]. The main manifestations of upper brachial plexus injury are that the shoulder joint cannot be abducted, the elbow joint cannot be flexed, the upper limb cannot rotate internally and externally, and the radial sensory disturbance, but the finger movement is still normal; the

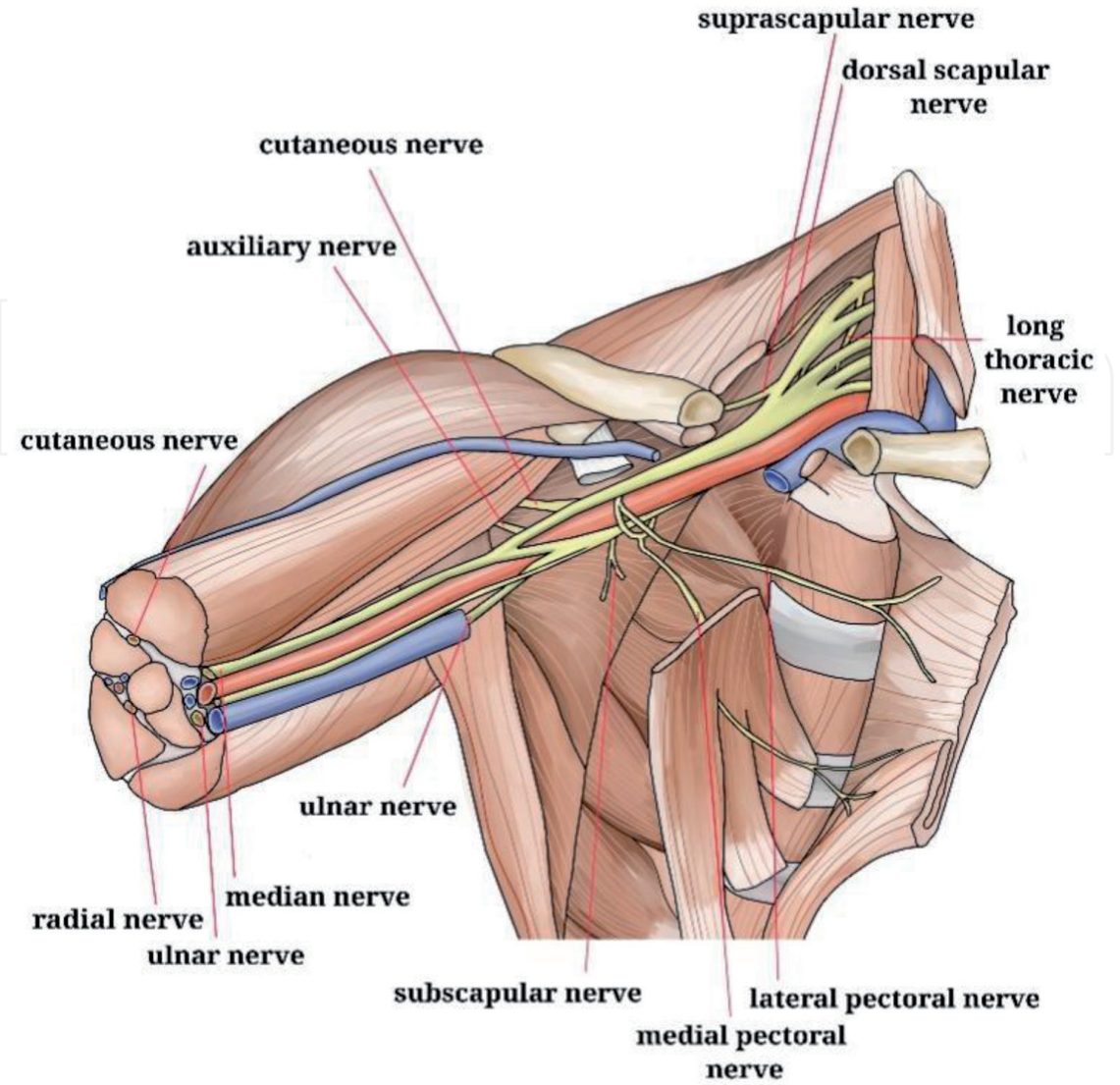

Figure 1.
Anatomy of the course of the brachial plexus in the armpit (drawn by Jia He).

main manifestations of lower brachial plexus injury were finger grasping dysfunction, sensory loss of ulnar skin of forearm and hand, but the activities of shoulder joint, elbow joint and wrist joint were normal; complete brachial plexus injury showed the disappearance of upper limb motor and sensory functions. The damage of different nerve branches also leads to the dysfunction of corresponding parts. For example, phrenic nerve injury can cause respiratory dysfunction, severe cases can cause apnea; musculocutaneous nerve injury can cause weakness in elbow flexion and weakened skin sensation on the outer forearm; axillary nerve injury mainly leads to deltoid muscle paralysis forming square shoulder; median nerve injury, as one of the common types of injury, is mainly manifested by the loss of sensory function on the radial side of the hand, forming "ape hand", as well as forearm pronation disorder; the main clinical manifestations of ulnar nerve injury is weakened wrist flexion ability and the distal end of the ring finger and little thumb cannot be flexed, resulting in the formation of "claw hand", which can also lead to loss of sensory function in the palm and the inner back of the hand; radial nerve injury mainly manifests as "wrist drop" caused by paralysis of the extensor muscle of the forearm, and accompanied by dorsal hand radial half and radial side of the two half finger proximal segment back skin sensory dysfunction (**Figure 2**).

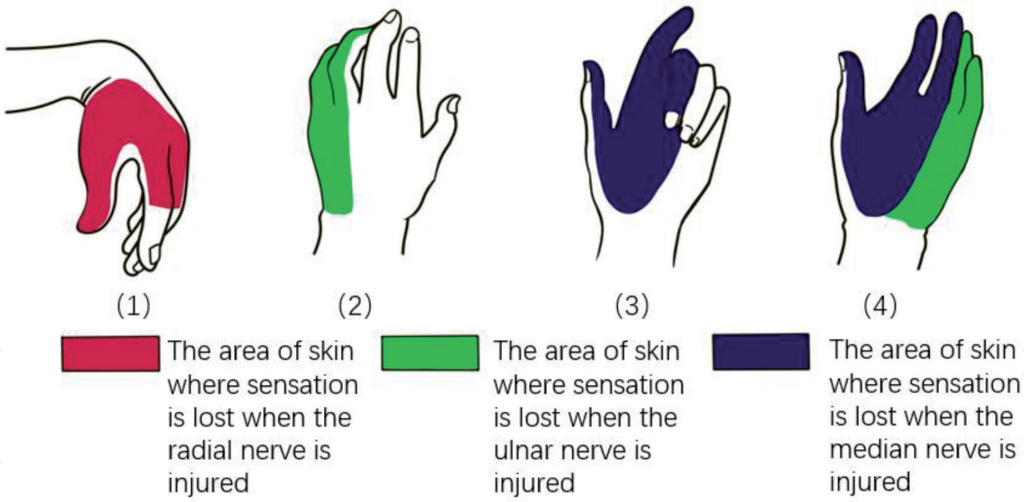

Figure 2.
(1). Wrist drop (radial nerve injury); (2). "Claw hand" (ulnar nerve injury); (3). Median nerve injury in hand; (4). "Ape hand" (median nerve injury and ulnar nerve injury) (drawn by Jia He).

3. Changes of regenerative microenvironment after brachial plexus injury

The repair process of BPI is related to many factors, such as the formation of regenerative microenvironment around the injury, the sprouting and extension of axons, the reinnervation of nerve to target tissue, axon regeneration and so on. The formation of regeneration microenvironment is an important factor affecting the repair of brachial plexus injury.

3.1 Establishment of nerve regeneration channels

After BPI, the axons and myelin sheath at the distal end of the injury degenerate and then disintegrate into nerve debris, Schwann cells (SCs) produce autophagy reaction, and eventually Wallerian degeneration occurs at the end of the nerve involved. In the early stage of injury, SCs can help macrophages to clear degenerative myelin debris, and the laminin secreted by it can form basement membranes to promote growth and provide channels, which can guide axons to grow rapidly in the right direction. The proliferating SCs form a solid cell cord (band of Büngner) in the nerve basal lamina enclosed by the basement membrane, which has a good guiding effect on the growth of nerve axons. The band of Büngner and nerve basal lamina can not only produce related molecules that promote axon regeneration, but also separate molecules that inhibit regeneration in the endoneurial tube, which can accelerate the regeneration and repair of injured nerve [7, 8].

3.2 Neurotrophic factor regulation

After BPI, SCs, nerve axons, fibroblasts and so on will produce a class of polypeptide called neurotrophic factors (NTFs), which have a variety of activities and can exert efficient physiological effects by binding to specific receptors on the surface of target cells [9]. It mainly includes 3 categories: ①. Neurotrophin, including nerve growth factor (NGF), brain-derived neurotrophin factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), and neurotrophin-6 (NT-6), neurotrophin-7 (NT-7) derived from non-mammals, etc. ②. Neurocytokinin, including ciliary neurotrophic factor (CNTF), interleukin-1,3,6 (IL-1,3,6), etc. ③. Fibroblast growth factor (FGF), and other NTFs such as glial cell line-derived neurotrophic factor

(GDNF), insulin like growth factor (IGF) and so on. These NTFs can play different roles in the regeneration and repair of injured brachial plexus, for example: ①. NGF combined with p75 can block p75 induced nerve cell death, thus can promote the intracellular signal transduction of injured nerve, which is conducive to accelerating the growth of axons and promoting the recovery of nerve function [10]. ②. The increased expression of BDNF and its tyrosine kinase receptor B (TrkB) mRNA can reshape synapses, restore neural pathways, and promote regeneration of axons and reconnection of injured muscles. ③. GDNF can nourish the axons and SCs of mature spinal cord, which is beneficial to axonal regeneration. It has been found that after sciatic nerve transection in rats, SCs can continuously express GDNF mRNA in nerve fibers for more than 5 months [11]. ④. Other studies have confirmed that NTFs can promote nerve cell regeneration and accelerate motor nerve conduction velocity to a certain extent [12].

3.3 Immune response

A series of immune responses after nerve injury can inhibit nerve regeneration and repair to a certain extent. The occurrence of immune response may be related to the following ways: ①. Nerve injury can destroy the blood-nerve barrier, resulting in the leakage of neurogenic antigens to nearby lymph nodes and the production of specific antibodies, which will enter the blood circulation and cause immune response. ②. There are antigen-presenting cells in the nerve tissue. After nerve injury, antigen-presenting cells can express MHC class II antigens on their cell membranes after ingesting neurological antigens, and are taken up by T cells in the nerves to produce an immune response. ③. After the antigen-presenting cells ingest neurogenic antigens, they can also be presented to T cells in the blood by intra-nerve microvascular endothelial cells to stimulate an immune response. The immune response will have a significant inhibitory effect on nerve regeneration and repair [13].

3.4 Inflammatory response

Wallerian degeneration occurs immediately after BPI. Within 24 hours after injury, SCs demyelinated by degrading myelin basic protein, and then macrophages migrated to the nerve injury through blood vessels [14]. During Wallerian degeneration, SCs and macrophages phagocytize the denatured myelin, which is conducive to nerve regeneration, and the occurrence of inflammatory reaction is mainly related to macrophages. Macrophages can participate in the phagocytosis of degenerated myelin, and secrete the active factor oncomodulin to promote the proliferation of SCs, thereby promoting axon regeneration. The glial cells activated at the nerve injury can secrete cytokines that promote or inhibit the inflammatory response, among which pro-inflammatory factors (such as IL-1, IL-2, IL −6 and tumor necrosis factor (TNF)), which are mainly produced in the first stage of Wallerian degeneration, and promote the recruitment of macrophages 2-3 days after nerve injury; while, anti-inflammatory factors (such as IL-10 and transforming growth factor β(TGF-β)) are produced after macrophage recruitment and attenuate the inflammatory response [15]. After BPI, SCs, macrophages, and mast cells can immediately produce endogenous TNF-α, and the rapidly increasing TNF-α in the lesion site can also recruit a large number of macrophages to swallow degeneration myelin. IL-1 is an important pro-inflammatory factor in the process of nerve injury, and its members include IL-1α, IL-1β and so on. After 5-6 hours of nerve injury, SCs that lose close contact with axons can quickly up-regulate IL-1α mRNA and IL-1α protein [16]. IL-1α can induce fibroblasts to accumulate in the

injured area and produce IL-6. IL-6 can enhance T cell activity and act on SCs, and participate in the regeneration of peripheral nerves by up-regulating pro-inflammatory response genes and immune protease subunits [17].

3.5 Hormonal regulation

After BPI, progesterone, thyroid hormone, adrenocorticotropic hormone and so on can participate in the repair of damaged nerves. Progesterone not only promotes the sciatic nerve of damaged male rats, but also binds to receptors to regulate the expression of SCs [18]. Thyroid hormone can play an important role in the growth and development of the central nervous system and the repair of peripheral nerve damage. It can make non-nerve cells produce NTFs to promote axon repair and regeneration, and can also act on SCs to maintain neuronal activity and promote nerve growth [19]. Adrenocorticotropic hormone can accelerate the regeneration of axons, which is beneficial to promote the regeneration and repair of injured nerves [20].

4. Treatment of brachial plexus injury

The treatment methods used vary according to the injury site, injury type, injury severity, and time after injury. The purpose of treatment is to reduce permanent disability and restore or improve upper limb function. The mild cases may be temporarily observed, functional exercises shall be performed, and re-examination shall be carried out regularly, while the severe cases may require treatment such as surgery.

4.1 General conservative treatment

General conservative treatment mainly includes local physical therapy, acupuncture, massage, comprehensive rehabilitation exercise, standardized electrical stimulation therapy, oral neurotrophic drugs, etc. In order to promote the regeneration of injured brachial plexus and prevent skeletal muscle denervation atrophy, so as to ensure that joints and muscles can work normally and move in the normal range of activity.

4.2 Surgical treatment

At present, the commonly used clinical surgical treatment methods for BPI mainly include nerve repair, nerve transplantation, nerve suture, neurolysis, nerve transfer (neuralization), tendon/muscle transfer, free functional muscle transfer (FFMT) and so on [21]. (1). Nerve suture: For patients with sharp cuts or penetrating injuries, the musculocutaneous nerve, lateral spinal cord or superior nerve trunk can be sutured directly end-to-end. (2). Exo-plexus nerve transfer: ①. Spinal accessory nerve (SAN) transfer: SAN is well used for nerve transfer because it has sufficient length and motor axons. Up to 95% of BPI patients retain SAN, which can be widely transferred to different targets to restore storage functions [22]. ②. Intercostal nerves (ICNs) transfer: Seddon first described the ICNs transfer, which borrowed ulnar nerve transplantation to transfer ICNs to the musculocutaneous nerve (MCN) to restore the elbow flexion function of patients with complete brachial plexus injury. Other surgeons may prefer to transfer the motor branches of ICNs directly to the biceps brachii branch of MCN to obtain more reliable motor

function recovery [23]. ③. Contralateral C_7 nerve root transfer: It is the safest surgical method for the treatment of brachial plexus root avulsion [24]. (3). Iintra-plexus nerve transfer: ①. Triceps branch of radial nerve (TRN) transfer: Since TRN runs along the proximal end of the upper arm with the radial and axillary nerves, transplanting one of the branches to the other nerve will not affect the normal function of its innervated area. Therefore, TRN is often transferred to axillary nerve to treat shoulder pain, shoulder subluxation, hand abduction insufficiency and other clinical symptoms caused by axillary nerve injury [25]. ②. Double nerve transfer method (Mackinnon's method, Oberlin II method): Oberlin et al. [26] elbow flexion dysfunction caused by brachial plexus root avulsion can be treated by transferring some of the ulnar nerve bundle branches located in the upper arm to the biceps muscle branch of the musculocutaneous nerve. ③. Medial pectoral nerve (MPN) transfer: can be used to treat obstetric brachial plexus injury [27]. ④. Transfer of brachialis muscle branch of the musculocutaneous nerve: This method has a good therapeutic effect whether it is to reduce the neuropathic pain of patients with simple brachial plexus inferior trunk injury, or to restore the function of finger holding [28]. (4). Gracilis FFMT: The gracilis muscle is considered to be a good BPI muscle metastasis due to its reliable proximal neurovascular pedicle and long tendon length, which can be used to treat elbow flexion difficulties caused by complete brachial plexus injury [29].

5. Development of functional electrical stimulation

5.1 Selection of functional electrical stimulation methods

At present, due to different stimulation methods and electrode placement positions, there are three main stimulation modes of FES: surface electrical stimulation, percutaneous electrical stimulation, and fully implanted electrical stimulation [30]. Each method has both advantages and disadvantages. (1). The advantage of surface electrical stimulation is that there is no cumbersome operation of embedding the electrode in the body, and no need to perform secondary operations for removing and needle electrodes, which reduces the possibility of trauma. This method is convenient and does not cause pain, but also has a very wide range of indications. However, it has the following disadvantages: ①. The patient will feel discomfort when the stimulation intensity is high and there will be a risk of scalding the skin, so the stimulation intensity and stimulation depth will become relatively limited, which leads to the ineffective stimulation of deep muscles, so that the effect produced is not very ideal. ②. Since most of the surface stimulation must be performed in the hospital, this will cause the interval between two stimulations to be too long, and the patient's compliance will become worse. ③. Stimulating a single muscle will also affect the contraction and relaxation of surrounding muscles, reducing its specificity. (2). The advantages of percutaneous electrical stimulation is that it is relatively simple and easy to implement, and has a wide range of indications, but it cannot stimulate the wounded skin, and there may be adverse reactions such as infection or skin damage. (3). The advantages of fully implanted electrical stimulation: ①. It can not only stimulate for a long time, but also maintain a high selective stimulation in the case of low power, and the effect is reliable. ②.It can avoid skin infection and damage caused by percutaneous stimulation. ③. It can avoid the inconvenience and discomfort caused by surface stimulation, and can prevent the defects that cannot be accurately located due to low specificity [30]. However, the implanted

electrode may also cause the electrode to shift or fall off, the battery is exhausted, the connection points between the electrodes are not firm and so on, which may cause complications such as infection of the electrode port and the body's rejection of the electrode [31].

5.2 Selection of functional electrical stimulation time

Electrical stimulation (ES) can promote injured nerve regeneration and functional recovery, but how to choose the best stimulation time is still controversial. Studies have shown that the immediate application of ES to the early injured nerve can accelerate axon regeneration and nerve function recovery [32], but this effect may only play in the initial stage of nerve regeneration, and will become smaller or even disappear after the beginning of nerve growth [33]. Some studies also believe that the above effects can also be achieved after a short delay in the FES start time [34]. The exact mechanism for the short-term delay of ES to accelerate neural recovery is still unclear, which may be related to the up-regulation of NGF expression by ES [35, 36]. As to whether ES can promote nerve regeneration at other time points after nerve injury, different researchers have put forward different opinions. For example, Zanakis [37] showed that once nerve regeneration starts, the presence or absence of electric field stimulation will not affect it. After animal experiments, Shen [38] found that FES can still promote nerve regeneration after 20 or even 60 days of nerve injury, and all the morphological, electrophysiological and neurological function indicators of peripheral nerves show a significant upward trend. For the stimulation of denervated muscles, it is generally believed that it should be performed immediately after denervation, in order to prevent muscle atrophy and restore motor function to the greatest extent.

5.3 Selection of functional electrical stimulation parameters

There are many factors that can affect the therapeutic effect of FES, and stimulation parameters are one of them. So we mainly discuss the settings of the following parameters. (1). Stimulation current: The commonly used stimulation currents in clinic mainly include electric field, electromagnetic field, intermediate frequency electrical stimulation, pulse electrical stimulation, constant weak direct current stimulation, etc. They can promote peripheral nerve repair, accelerate nerve fiber regeneration, and prevent muscle atrophy. (2). Stimulation intensity: Different intensities of es will have different effects on the regeneration of nerve fibers. For example, using 1 mA current to stimulate the injured nerve can significantly increase the nerve conduction speed, but the current intensity of 4 mA has a detrimental effect on regenerating nerve fibers [39]. For the stimulation of denervated muscles, due to the large amount of fat and connective tissue present in it, which have a strong current transfer ability, it can reduce the current reaching the muscle cells, so that muscle cells must be stimulated by high current or even exponential current to reach the excited state. (3). Stimulation pulse: The research found that the pulse used for stimulation can be divided into single-phase pulse and two-phase pulse. Because monophasic pulses apply energy to the body, and this energy will never be removed. Therefore, it may cause potential damage to the stimulated tissue, while biphasic pulses use pulses of different amplitudes alternately on the body surface Stimulation, which can significantly reduce the damage to the body [40]. In summary, the optimal parameters of FES have not yet been unified, and further research is still needed. At the same time, the effects of early, middle and late nerve recovery must be analyzed to achieve satisfactory results.

6. Application of functional electrical stimulation in brachial plexus injury

6.1 Localization effect of functional electrical stimulation in interscalene brachial plexus nerve block

Interscalene brachial plexus nerve block anesthesia is a common local nerve block anesthesia method in clinic, which is often used in the operation anesthesia of upper limb dysfunction caused by BPI. Traditional interscalene brachial plexus nerve block is mainly based on anatomical landmarks and the clinical experience of the anesthesiologist, and the success rate and effect are very different. In the process of anesthesia operation, blind detection of nerve position with puncture needle may lead to anesthesia failure, and patients may also have nerve injury phenomenon, which seriously affects the success rate and safety of Interscalene brachial plexus nerve block anesthesia. The use of neural electrical stimulator can optimize the above problems [41]. Zhao Xiaojuan et al. [42] 50 patients who needed upper limb surgery under Interscalene brachial plexus nerve block anesthesia into observation group and control group with 25 cases in each group. Before anesthesia, the two groups of patients were monitored by ECG, peripheral veins were opened, and midazolam 2 mg was administered intravenously. The patient was placed in a supine position, the affected limb was placed next to the trunk, and the head was tilted to the opposite side. The use of low-frequency ES can better increase the level of cAMP in nerve cells, thereby inducing cells to conduct synthetic reactions. This response can promote dorsal root ganglion (DRG) growth by up-regulating cell growth-related proteins and cytoskeleton proteins [43]. The initial current of the stimulator is set to 1.0 mA and the frequency is 1.0 Hz. When the puncture needle is close to the nerve trunk, it can cause the effect muscles innervated by the nerve to contract. Adjust the position of the stimulating needle to the median nerve or radial nerve or ulnar nerve of the patient's upper limbs. When the current is gradually reduced to 0.2-0.3 mA, there will be no effective muscle contraction. After confirming that there is no blood sucked back, inject 1% lidocaine into the extension tube connected to the insulated needle. In the control group, the traditional allosensory method was used for interscalene brachial plexus block. After observing various anesthesia indicators, it was found that the overall excellent and good rate of the observation group was higher than that of the control group, while the anesthesia operation time and the incidence of adverse reactions were significantly lower than that of the control group. It can be seen that the use of nerve stimulator to guide interscalene brachial plexus nerve block can significantly shorten the time of anesthesia, increase the success rate of anesthesia, and reduce the incidence of adverse reactions. It has very important clinical significance for upper limb surgery [44].

6.2 Rehabilitation effect of functional electrical stimulation in brachial plexus injury

After clinical practice, it was found that conventional conservative treatment combined with standardized electrical stimulation can achieve better rehabilitation effects. Standardized electrical stimulation therapy refers to the combination of low-frequency electrical stimulation and medium-frequency electrical stimulation, and then placing electrodes on the corresponding damaged muscles of the patient to promote the regeneration and repair of injured nerves and prevent denervation of skeletal muscles. At present, BPI comprehensive rehabilitation training takes many forms. For example, Liu Suzhe [45] randomly divided 100

children with obstetric brachial plexus palsy (OBPP) into two groups, one of which received routine rehabilitation (oral neurotrophic drugs, self-functional exercise at home, etc.), while the other group used a neuromuscular electrical stimulator on the basis of conventional rehabilitation treatment. The results showed that the addition of electromyographic stimulation can significantly improve the prognostic rate of children with affected limbs. Liu Hui [46] took 36 children who were treated for brachial plexus injury as the research object and were randomly divided into control group and experimental group, with 18 cases in each group. The control group was treated with acupuncture and the experimental group was combined with neuromuscular electrical stimulation on the basis of the control group. A comparative analysis of the treatment effects of the two groups of children found that the implementation of neuromuscular electrical stimulation combined with acupuncture therapy has a significant therapeutic effect and can effectively restore the function of the injured muscles of the children. Gu Yudong et al. [47] took 43 BPI patients admitted to their hospital as research subjects and randomly divided them into a treatment group and a control group. The 21 patients in the treatment group received comprehensive rehabilitation treatment such as percutaneous nerve stimulation and intermediate frequency electrotherapy. The control group did not take such treatment measures. The results of the study showed that compared with the observation group, the branch and total branch injury function scores of the treatment group were significantly higher than those of the control group, and the electromyography results showed that the receptor nerve regeneration potential appeared earlier in the treatment group. The above only exemplified part of the electrical stimulation combined with conventional rehabilitation training, and the results all show that such comprehensive therapy has played a better role in repairing brachial plexus injury. In addition, FES also has the characteristics of simple operation, safe and effective, no side effects and so on, it can be widely used in clinical practice.

6.3 Therapeutic effect of functional electrical stimulation on neuropathic pain caused by brachial plexus injury

In a prospective epidemiological survey, it was found that 60 of the 107 BPI patients who were diagnosed with neuropathic pain using the DH4 questionnaire were diagnosed. Neuropathic pain will have a certain impact on the patient's mind and quality of life [48]. At present, the commonly used clinical treatment measures are mainly to control symptoms by taking painkillers, but the results obtained are not optimistic, and there is a problem of treating the symptoms but not the root cause. Therefore, it is especially important to find a way to relieve or even eradicate neuralgia. Sun Yanli et al. [49] gave 31 patients with BPI combined with neuralgia to improve circulation, nutritional nerves, pain relief and other conventional treatments, and then supplemented with electrical stimulation (waveform: triangle wave, intensity: 20-30 mA, frequency: 50-100 Hz, pulse width: 10MS, time: 1 time/d, 30 min/time, 10 times as a course of treatment). After using the visual analogue scoring method, pain assessment form, and sleep self-rating scale to assess the degree of pain, it was found that after 3-4 electrical stimulation treatments, 93.5% of patients reported that it was effective, and the number and duration of burst pain were significantly reduced compared to before treatment. After 2 treatment cycles, all patients have reduced the use of painkillers to varying degrees, and 96.7% of patients have controlled their pain in an ideal state. This study shows that the use of FES can relieve neuropathic pain caused by BPI to a certain extent, and can improve the quality of life of patients.

7. Physiological mechanism of functional electrical stimulation for brachial plexus injury

The mechanism by which FES exerts the above effects is not clear, but a large number of studies have shown that it is closely related to factors such as promoting the secretion of SCs and NTFs, promoting axon regeneration, increasing blood supply, protecting muscle fibers, and reducing muscle fatigue.

7.1 Physiological mechanism of functional electrical stimulation promoting nerve regeneration

The electric field generated by ES can stimulate SCs to crawl, migrate, proliferate and divide [50], making them further secrete NTFs such as BDNF, NGF and NT 4 / 5 [51, 52]. Moreover, the electric field has a certain tendency to the structural proteins, microfilaments and microtubules of axons, which can not only improve the nerve growth speed, but also make the broken axons grow into the distal nerve stump along the correct direction [53]. When the axon enters the neural tube of the distal nerve stump, the number of axons passing through the repair site can be increased to promote the increase in the number of motor neurons, sensory neurons and the density of regenerative nerves [43], thus maximizing nerve function degree of recovery.

ES can increase the level of Ca^{2+} by inducing cell membrane depolarization and opening voltage-gated calcium channels, and the increase of Ca^{2+} can raise the expression of BDNF and its TrkB mRNA, which is most closely related to motor neuron regeneration [54], It can promote the reconnection of axons and muscles, accelerate nerve conduction speed and enhance muscle fiber vitality, and then restore damaged nerve function. Through research, it is found that the main target of ES in downstream pathways is cyclic adenosine monophosphate (cAMP). The use of low-frequency ES can better increase the level of cAMP in nerve cells and induce cells to undergo synthetic reactions, which can upregulate the expression of cells growth-related proteins and cytoskeleton proteins (including actin, tubulin, and growth-associated protein 43) [55] to promote Dorsal root ganglion (DRG) neurite outgrowth. At the same time, ES can also induce cAMP to activate phosphokinase A (PKA), and activated PKA can mediate the phosphorylation of cAMP response element binding protein (CREB) [56], which in turn activates downstream pathways and increases the expression of BDNF. When BNDF rises to a certain level, the continuous increase of cAMP can be maintained by inhibiting phosphodiesterase [57]. Therefore, as long as a short electrical stimulation can cause a series of closed-loop reactions that promote cAMP to rise and maintain a certain level.

7.2 Physiological mechanism of functional electrical stimulation inhibiting skeletal muscle atrophy

Using NMES to stimulate the damaged muscles can make the muscles contract passively and rhythmically, which can expand the nutritional blood vessels of the damaged brachial plexus. The increased blood flow and circulatory stretching caused by vasodilation may stimulate the production of vascular endothelial growth factor. These growth factors can reduce the rate of vascular degeneration and induce angiogenesis, which can accelerate the metabolism of denervated muscles, provide various nutritional factors required for nerve regeneration, and remove harmful substances to prevent them from accumulating in muscles [58], and will not affect the reinnervation of nerves, at the same time, it can accelerate the establishment

of effective contact between axons and distal effectors, restore the ultrastructure of myofibrils and membrane Ca^{2+} channels, thereby reducing muscle atrophy and improving muscle function [59]. There are also certain differences in the effects of different intensities of electrical stimulation on damaged muscles and the mechanism of action, For example, medium frequency electrotherapy is a positive and negative alternating current, which has no electrolytic effect on body tissues, there is no acid–base reaction under the electrode, which can prevent chemical irritation to the skin and reduce skin resistance. When the current intensity is high, the current can directly reach the deep tissues, and the distance between cells and tissues can be increased when used in the early stage of injury, thereby effectively preventing the adhesion of muscle fibers, tissue fibers and nerve fibers, and ultimately achieving significant relief of muscle pain and reduction the purpose of tissue adhesion and relieving scar contracture secondary to brachial plexus surgery [60]. High frequency electrical stimulation plays an important role in maintaining the contractile function of type II muscle fibers, reducing muscle fatigue and preventing muscle atrophy [61].

Over time, most patients with BPI will experience varying degrees of muscle atrophy, accompanied by programmed apoptosis of denervated skeletal muscle cells [62]. When muscle atrophy reaches a certain degree, new nerves will not be accepted and irreversible dysfunction will occur [63]. Paillard et al. [64] and others believe that ES can activate satellite cells and promote the expression of myoblast related biomarkers, which can reduce the expression of ubiquitin ligase gene related to muscle atrophy, so as to remodel muscle fibers. Honda et al. [65] found that muscle contraction induced by ES can prevent the reduction of muscle nucleus caused by apoptotic changes, thereby reducing the aggregation of macrophages. These changes may prevent the signal transduction of fibroblasts into myofibroblasts through the IL-1β/TGF-β1 pathway, thus achieving the goal of inhibiting muscle fibrosis and atrophy. FES can also induce mitochondrial generation, improve mitochondrial function and prevent mitochondrial enzyme inactivation, which can increase the energy supply of muscle cells and prevent rapid atrophy and apoptosis of skeletal muscle [47].

8. Conclusion

In recent years, with the frequent occurrence of accidental injuries such as car accidents, external force pulling, and heavy object crushing, BPI has shown an upward trend year by year. Mild cases may have temporary upper limb dysfunction with tingling or burning sensation and arm numbness and weakness; severe cases may have varying degrees of muscle paralysis or atrophy of upper limbs, accompanied by weakened or disappeared motor and sensory functions, and even appear complete loss of upper limb function. Therefore, repairing the damaged brachial plexus and promoting its functional recovery is an important problem that needs to be solved urgently. The solution of this problem is related to the establishment of nerve regeneration channels, neurotrophic factor regulation, immune response, inflammatory response, hormone regulation and other local micro The formation of the environment is closely related. At present, the commonly used clinical surgical treatment methods for BPI mainly include nerve transplantation, nerve suture, nerve transfer (neuralization), etc. However, after surgery, combined with conventional treatments such as FES can achieve a best rehabilitation effect. FES can play a role in all aspects of BPI treatment. For example, in the repair of brachial plexus injury, FES combined with ultrasound can accurately locate the nerve block site and shorten the anesthesia time; in the process of postoperative rehabilitation,

combined with conventional conservative treatment can promote the regeneration of injured brachial plexus and inhibit denervated skeletal muscle atrophy. In addition, FES can relieve neuropathic pain caused by BPI.

Although FES has a certain promoting effect in the various processes of brachial plexus repair, each BPI patient's blood supply, degree of injury, psychological endurance and self-rehabilitation ability are different, and FES itself also has ①. Cost problem. ②. Electrode material selection. ③. Optimal combination of electrical stimulation parameters. ④. Optimal stimulus site selection and other problems have not been resolved, so the efficiency of functional recovery still cannot reach the inherent motor ability of human beings. Therefore, we hope that in future research, we can conduct in-depth studies on the adjustment of the frequency, amplitude, and pulse width of electrical stimulation, as well as at which stage of nerve repair to start electrical stimulation, so as to overcome the problems of nerve regeneration and nerve function repair.

Acknowledgements

The completion of the chapter is attributed to many people's support and encouragement. First and foremost, I want to thank the Key Laboratory of Human-Machine-Intelligence Synergic System, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (Director, Professor Guang Lin Li), and Guangdong-Hong Kong-Macao Joint Laboratory of Human-Machine Intelligence-Synergy Systems.

Also, I would like to express my sincere gratitude to the fund supports of National Natural Science Foundation of China (Grant Nos. 81960419; 81760416 and 81927804) and also to. Last my thanks would go to my student, Ms. Zijun Zhang and Mr. Xinkuan Liao who search and collect references for the completion of this chapter.

Nomenclature

BPI	Brachial Plexus Injury
FES	Functional Electrical Stimulation
NMES	Neuromuscular Electrical Stimulation
SCs	Schwann Cells
NTFs	Neurotrophic Factors
NGF	Nerve Growth Factor
BDNF	Brain-Derived Neurotrophin Factor
NT	Neurotrophin
CNTF	Ciliaryneurotrophic Factor
IL	Interleukin
FGF	Fibroblast Growth Factor
GDNF	Glial Cell Line-derived Neurotrophic Factor
IGF	Insulin-Like Growth Factor
TrkB	Tyrosine Kinase Receptors
TNF	Tumor Necrosis Factor
TGF-β	Transforming Growth Factor β
FFMT	Free Functional Muscle Transfer
SAN	Spinal Accessory Nerve
MCN	Musculocutaneous Nerve
ICNs	Intercostal Nerves

TRN	Triceps Branch of Radial Nerve
MPN	Medial Pectoral Nerve
ES	Electrical Stimulation
OBPP	Obstetric Brachial Plexus Palsy
cAMP	Cyclic Adenosine Monophosphate
DRG	Dorsal Root Ganglion
PKA	Protein Kinase A
CREB	Cyclic-AMP Response Binding Protein

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References

[1] Rich JA, Newell A, Williams T. Traumatic brachial plexus injury rehabilitation using neuromuscular electrical muscle stimulation in a polytrauma patient. BMJ Case Reports. 2019;12(12):e232107. DOI: 10.1136/bcr-2019-232107

[2] Lieberson WT, Holmquest HJ, D. Scott, et al. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. Archives of Physical Medicine and Rehabilitation. 1961;42:101-105. DOI: 10.2307/2656978

[3] Sun B, Zhou ZM, Zhong YJ. Clinical effect of functional electrical stimulation on hemiplegia in stroke patients. Chinese Journal of Practical Nervous Diseases. 2020; 23(12):1095-1099. DOI: CNKI:SUN:HNSJ.0.2020-12-019

[4] Elzinga K, Tyreman N, Ladak A, et al. Brief electrical stimulation improves nerve regeneration after delayed repair in Sprague Dawley rats. Exp Neurol. 2015;269:142-153. DOI: 10.1016/j.expneurol.2015.03.022

[5] Pejkova S, Filipce V, Peev I, et al. Brachial Plexus Injuries - Review of the Anatomy and the Treatment Options. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2021;42(1):91-103. DOI: 10.2478/prilozi-2021-0008

[6] Hsueh YH, Tu YK. Surgical reconstructions for adult brachial plexus injuries. Part I: Treatments for combined C5 and C6 injuries, with or without C7 injuries. Injury. 2020;51(4):787-803. DOI: 10.1016/j.injury.2020.02.076

[7] Jang SY, Shin YK, Park SY, et al. Autophagic myelin destruction by Schwann cells during Wallerian degeneration and segmental demyelination. Glia. 2016;64(5):730-742. DOI: 10.1002/glia.22957

[8] Barton MJ, John JS, Clarke M, et al. The Glia Response after Peripheral Nerve Injury: A Comparison between Schwann Cells and Olfactory Ensheathing Cells and Their Uses for Neural Regenerative Therapies. Int J Mol Sci. 2017 Jan 29;18(2):287. DOI: 10.3390/ijms18020287

[9] Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci. 2003 Apr;4(4):299-309. DOI: 10.1038/nrn1078

[10] Chen ZY, Chai YF, Cao L, et al. Glial cell line-derived neurotrophic factor enhances axonal regeneration following sciatic nerve transection in adult rats. Brain Res. 2001;902(2):272-276. DOI: 10.1016/s0006-8993(01)02395-2

[11] Omura T, Sano M, Omura K, et al. Different expressions of BDNF, NT3, and NT4 in muscle and nerve after various types of peripheral nerve injuries. J Peripher Nerv Syst. 2005;10(3):293-300. DOI: 10.1111/j.1085-9489.2005.10307.x

[12] Faustino C, Rijo P, Reis CP. Nanotechnological strategies for nerve growth factor delivery: Therapeutic implications in Alzheimer's disease. Pharmacol Res. 2017 Jun;120:68-87. DOI: 10.1016/j.phrs.2017.03.020

[13] Song KK, Zhang K, Jia L. The microenvironment and repair methods of peripheral nervous system injury. J Clin Rehabil Tis Eng Res. 2021;No.933(04):165-170. DOI: CNKI:SUN:XDKF.0.2021-04-031

[14] Austin PJ, Moalem-Taylor G. The neuro-immune balance in neuropathic pain: Involvement of inflammatory immune cells, immune-like glial cells and cytokines. Journal of Neuroimmunology. 2010;229(1-2):26-50. DOI: 10.1016/j.jneuroim.2010.08.013

[15] Rotshenker S. Wallerian degeneration: the innate-immune response to traumatic nerve injury. Journal of Neuroinflammation. 2011;8(1):1-14. DOI: 10.1186/1742-2094-8-109

[16] Nadeau S, Filali M, Zhang J, et al. Functional recovery after peripheral nerve injury is dependent on the pro-inflammatory cytokines IL-1βand TNF: implications for neuropathic pain. J Neurosci. 2011;31(35):12533-12542. DOI: 10.1523/JNEUROSCI.2840-11.2011

[17] Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. J Neuroinflammation. 2011;8:110. DOI: 10.1186/1742-2094-8-110

[18] Yu HJ, Fei J, Chen XS, et al. Progesterone attenuates neurological behavioral deficits of experimental autoimmune encephalomyelitis through remyelination with nucleus-sublocalized Olig1 protein. Neurosci Lett. 2010;476(1):42-45. DOI: 10.1016/j.neulet.2010.03.079

[19] Li WW, Le Goascogne C, Schumacher M, et al. Type 2 deiodinase in the peripheral nervous system: induction in the sciatic nerve after injury. Neuroscience. 2001;107(3):507-518. DOI: 10.1016/s0306-4522(01)00362-1

[20] Mohammadi R, Yadegarazadi MJ, Amini K. Peripheral nerve regeneration following transection injury to rat sciatic nerve by local application of adrenocorticotropic hormone. J Craniomaxillofac Surg. 2014;42(6):784-789. DOI: 10.1016/j.jcms.2013.11.012

[21] Bertelli JA, Ghizoni MF. Combined injury of the accessory nerve and brachial plexus. Neurosurgery. 2011;68(2):390-395; discussion 396. DOI: 10.1227/NEU.0b013e318201d7d9

[22] Xiao C, Lao J, Wang T, et al. Intercostal nerve transfer to neurotize the musculocutaneous nerve after traumatic brachial plexus avulsion: a comparison of two, three, and four nerve transfers. J Reconstr Microsurg. 2014;30(5):297-304. DOI: 10.1055/s-0033-1361840

[23] Songcharoen P, Wongtrakul S, Spinner RJ. Brachial plexus injuries in the adult. nerve transfers: the Siriraj Hospital experience. Hand Clin. 2005;21(1):83-89. DOI: 10.1016/j.hcl.2004.10.002

[24] Gu YD, Zhang GM, Chen DS, et al. Seventh cervical nerve root transfer from the contralateral healthy side for treatment of brachial plexus root avulsion. J Hand Surg Br. 1992;17(5):518-521. DOI: 10.1016/s0266-7681(05)80235-9

[25] Oberlin C, Béal D, Leechavengvongs S, et al. Nerve transfer to biceps muscle using a part of ulnar nerve for C5-C6 avulsion of the brachial plexus: anatomical study and report of four cases. J Hand Surg Am. 1994;19(2):232-237. DOI: 10.1016/0363-5023(94)90011-6

[26] Blaauw G, Slooff AC. Transfer of pectoral nerves to the musculocutaneous nerve in obstetric upper brachial plexus palsy. Neurosurgery. 2003;53(2):338-341. DOI: 10.1227/01.neu.0000073420.66113.66

[27] Ray WZ, Yarbrough CK, Yee A, et al. Clinical outcomes following brachialis to anterior interosseous nerve transfers. J Neurosurg. 2012;117(3):604-609. DOI: 10.3171/2012.6.JNS111332

[28] Maldonado AA, Kircher MF, Spinner RJ, et al. Free Functioning Gracilis Muscle Transfer versus Intercostal Nerve Transfer to Musculocutaneous Nerve for Restoration of Elbow Flexion after

Traumatic Adult Brachial Pan-Plexus Injury. Plast Reconstr Surg. 2016;138(3):483e-488e. DOI: 10.1097/PRS.0000000000002471

[29] Liu SZ, Zhao S, Zhao WY. et al. Effect of early rehabilitation on neonatal brachial plexus injury. J Hebei Med Univ. 2016;37(1):27-29. DOI: 10.3969/j.issn.1007-3205.2016.01.008

[30] Popovic MR, Popovic DB, Keller T. Neuroprostheses for grasping. Neurol Res. 2002 Jul;24(5):443-452. DOI: 10.1179/016164102101200311

[31] Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J Neurosurg. 2004;100(3 Suppl Spine):254-67. DOI: 10.3171/spi.2004.100.3.0254

[32] Huang J, Lu L, Hu X, et al. Electrical stimulation accelerates motor functional recovery in the rat model of 15-mm sciatic nerve gap bridged by scaffolds with longitudinally oriented microchannels. Neurorehabil Neural Repair. 2010;24(8):736-745. DOI: 10.1177/1545968310368686

[33] Asensio-Pinilla E, Udina E, Jaramillo J, Navarro X. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. Exp Neurol. 2009;219(1):258-265. DOI: 10.1016/j.expneurol.2009.05.034

[34] Yeh CC, Lin YC, Tsai FJ, et al. Timing of applying electrical stimulation is an important factor deciding the success rate and maturity of regenerating rat sciatic nerves. Neurorehabil Neural Repair. 2010;24(8):730-735. DOI: 10.1177/1545968310376758

[35] Al-Majed AA, Brushart TM, Gordon T. Electrical stimulation accelerates and increases expression of BDNF and trkB mRNA in regenerating rat femoral motoneurons. Eur J Neurosci. 2000;12(12):4381-4390. DOI: 10.1111/j.1460-9568.2000.01341.x

[36] Al-Majed AA, Tam SL, Gordon T. Electrical stimulation accelerates and enhances expression of regeneration-associated genes in regenerating rat femoral motoneurons. Cell Mol Neurobiol. 2004;24(3):379-402. DOI: 10.1023/b:cemn.0000022770.66463.f7

[37] Zanakis MF. Differential effects of various electrical parameters onperi pheral and central nerve regeneration. Acupunct Electrother Res. 1990;15(3-4):185-191. DOI: info:doi/10.3727/036012990816358199

[38] Shen NJ, Wang SC. Using a direct current electrical field to promotespinal-cord regeneration. J Reconstr Microsurg. 1999;15(6):427-431. DOI: 10.1055/s-2007-1000122

[39] Lu MC, Tsai CC, Chen SC, et al. Use of electrical stimulation at different current levels to promote recovery after peripheral nerve injury in rats. J Trauma. 2009;67(5):1066-1072. DOI: 10.1097/TA.0b013e318182351a

[40] Marquez-Chin C, Popovic MR. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. Biomed Eng Online. 2020;19(1):34. DOI: 10.1186/s12938-020-00773-4

[41] Joubert KE. Electrical nerve stimulation as an aid to the placement of a brachial plexus block. J S Afr Vet Assoc. 2002;73(4):216-218. DOI: 10.4102/jsava.v73i4.590

[42] Zhao XJ, Lu SC, Xu P. Application of Nerve Stimulation Instrument Guided Interscalene Brachial Plexus Nerve Block Anesthesia in Upper Limb Surgery. Chin Cont Med Edu. 2017,

009(023):72-73. DOI:10.3969/j.issn.1674-9308.2017.23.037

[43] Shapira Y, Midha R. Shocking therapy: Brief electrical stimulation for delayed nerve repair. Exp Neurol. 2015;271:524-525. DOI: 10.1016/j.expneurol.2015.07.015

[44] Chen YL, Deng M, Li JG, et al. Clinical study of percutaneous positioning of nerve stimulator for intermuscular sulcus brachial plexus block. Chinese Journal of Practical Nervous Diseases. 2016;19(01):82-83. DOI: 10.3969/j.issn.1673-5110.2016.01.045

[45] Liu SZ, Zhao S, Zhao WY, et al. Observation on the effect of early rehabilitation on neonatal brachial plexus injury. Journal of Hebei Medical University. 2016;37(01):27-29. DOI: 10.3969/j.issn.1007-3205.2016.01.008

[46] Liu H. Effect of neuromuscular electrical stimulation combined with acupuncture in rehabilitation treatment of brachial plexus injury in children. Guide of China Medicine. 2017;15(14):104-105. DOI: CNKI:SUN:YYXK.0.2017-14-083

[47] Zhou JM, Gu YD, Xu XJ, et al. Clinical research of comprehensive rehabilitation in treating brachial plexus injury patients. Chinese Medical Journal. 2012;125(14):2516-2520. DOI: 10.3760/cma.j.issn.0366-6999.2012.14.022

[48] Ciaramitaro P, Padua L, Devigili G, et al. Prevalence of Neuropathic Pain in Patients with Traumatic Brachial Plexus Injury: A Multicenter Prospective Hospital-Based Study. Pain Med. 2017;18(12):2428-2432. DOI: 10.1093/pm/pnw360

[49] Sun YL, Lin CX, Zhao XC, et al. .Application of electrical stimulation in the nursing and management of patients with brachial plexus injury and pain. World Latest Medicine Information. 2017;17(A3):170-171. DOI: CNKI:SUN:WMIA.0.2017-A3-116

[50] Zuo KJ, Shafa G, Antonyshyn K, et al. A single session of brief electrical stimulation enhances axon regeneration through nerve autografts. Exp Neurol. 2020;323:113074. DOI: 10.1016/j.expneurol.2019.113074

[51] Cobianchi S, Casals-Diaz L, Jaramillo J, et al. Differential effects of activity dependent treatments on axonal regeneration and neuropathic pain after peripheral nerve injury. Exp Neurol. 2013;240:157-167. DOI: 10.1016/j.expneurol.2012.11.023

[52] Huang J, Zhang Y, Lu L, et al. Electrical stimulation accelerates nerve regeneration and functional recovery in delayed peripheral nerve injury in rats. Eur J Neurosci. 2013;38(12):3691-3701. DOI: 10.1111/ejn.12370

[53] He L, Lv MX, Ruan L, et al. An animal experimental study on low-frequency electrical stimulation to promote peripheral nerve regeneration and functional recovery. J Hebei Med Univ.2019;40(4):396-400,405. DOI:10.3969/j.issn.1007-3205.2019.04.005.

[54] Wenjin W, Wenchao L, Hao Z, et al. Electrical stimulation promotes BDNF expression in spinal cord neurons through Ca(2+)- and Erk-dependent signaling pathways. Cell Mol Neurobiol. 2011;31(3):459-467. DOI: 10.1007/s10571-010-9639-0

[55] Urbanchek MG, Kung TA, Frost CM, et al. Development of a Regenerative Peripheral Nerve Interface for Control of a Neuroprosthetic Limb. Biomed Res Int. 2016;2016:5726730. DOI: 10.1155/2016/5726730

[56] Aglah C, Gordon T, Posse de Chaves EI. cAMP promotes neurite outgrowth and extension through

protein kinase A but independently of Erk activation in cultured rat motoneurons. Neuropharmacology. 2008;55(1):8-17. DOI: 10.1016/j.neuropharm.2008.04.005

[57] Batty NJ, Fenrich KK, Fouad K. The role of cAMP and its downstream targets in neurite growth in the adult nervous system. Neurosci Lett. 2017;652:56-63. DOI: 10.1016/j.neulet.2016.12.033

[58] Nakagawa K, Tamaki H, Hayao K, et al. Electrical Stimulation of Denervated Rat Skeletal Muscle Retards Capillary and Muscle Loss in Early Stages of Disuse Atrophy. Biomed Res Int. 2017;2017:5695217. DOI: 10.1155/2017/5695217

[59] Willand MP, Holmes M, Bain JR, et al. Electrical muscle stimulation after immediate nerve repair reduces muscle atrophy without affecting reinnervation. Muscle Nerve. 2013;48(2):219-225. DOI: 10.1002/mus.23726

[60] Zhuang Y, Sun KX, Zhou JM, et al. Clinical observation on the treatment of brachial plexus injury by electroacupuncture combined with rehabilitation training. Chinese Journal of Rehabilitation. 2016;31(2):149-150. DOI: 10.3870/zgkf.2016.02.022

[61] Williams HB. A clinical pilot study to assess functional return following continuous muscle stimulation after nerve injury and repair in the upper extremity using a completely implantable electrical system. Microsurgery. 1996;17(11):597-605. DOI: 10.1002/(SICI)1098-2752(1996)17:113.0.CO;2-M

[62] Gordon T. Electrical Stimulation to Enhance Axon Regeneration After Peripheral Nerve Injuries in Animal Models and Humans. Neuro therapeutics. 2016;13(2):295-310. DOI: 10.1007/s13311-015-0415-1

[63] Menorca RM, Fussell TS, Elfar JC. Nerve physiology: mechanisms of injury and recovery. Hand Clin. 2013;29(3):317-330. DOI: 10.1016/j.hcl.2013.04.002

[64] Paillard, and Thierry. "Muscle plasticity of aged subjects in response to electrical stimulation training and inversion and/or limitation of the sarcopenic process." Ageing Research Reviews (2018):S1568163718300667.

[65] Honda Y, Tanaka N, Kajiwara Y, et al. Effect of belt electrode-skeletal muscle electrical stimulation on immobilization-induced muscle fibrosis. PLoS One. 2021;16(5):e0244120. DOI: 10.1371/journal.pone.0244120